

## **EXHIBIT B**

## On the Unpredictability of Odor

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## Keywords:

fragrances · olfaction · receptors · structure–activity relationships

**T**he relationship between molecular structure and odor has fascinated and puzzled chemists for more than a century. Despite a great deal of research on structure–odor relationships, prediction of the odor of a novel molecule remains a statistical exercise and models only provide a probability of the character, threshold, and intensity. Surprises are still commonplace, and serendipity continues to be an important factor in the discovery of novel fragrant molecules. Recent advances in our understanding of the mechanism of olfaction provide an explanation for this and suggest that our ability to predict odor properties of molecules will not improve significantly in the near future.

## 1. Introduction

The search to correlate the molecular structure and the odor character of a chemical compound has a long recorded history. In ancient Greece, the proponents of Democritus' atomic theory proposed that the atoms of sweet-smelling substances had smooth surfaces whereas those of acidic materials had sharp points that pricked and irritated the nose. Since the development of synthetic organic chemistry in the 19th century, chemists have sought a clearer understanding of the relationship between molecular structure and the odor of a molecule, largely with the intention to design novel molecules with desirable odor properties.

However, this search for understanding has proved to be a very difficult task. There are many puzzling observations that often have no simple or obvious explanation. For example, on one hand, quite different molecules can have similar odors, whereas, on the other hand, similar molecules can have dissimilar odors. Thus, despite the significant differences in their structures, muscone (1),<sup>[1]</sup> musk ketone (2),<sup>[2]</sup> Trascollide (3),<sup>[3]</sup> and Helvetolide (4)<sup>[4]</sup> all have similar musk odors (Figure 1), whereas the two very similar structures 5 and 6 have very different organoleptic properties: 5 has an intense urinous character while 6 is odorless.<sup>[5]</sup>

Sometimes, the functional group present in an odorant is all-important. For example, the ester group is often associated with a fruity character.<sup>[6]</sup> Thus, both Fruitate (7)<sup>[7]</sup> and Manzanate (8)<sup>[8]</sup> have distinctly fruity odors

despite the differences in size and structural complexity between them (Figure 2). However, in other cases, the functional group seems unimportant: for example, structures 9–12 all have camphoraceous odors.<sup>[9]</sup>

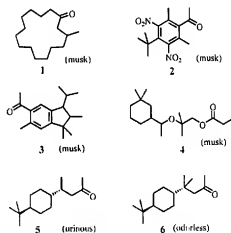


Figure 1. Different molecules, similar odors; and vice versa.

In many instances factors such as these can be brought together in triads, where the odd molecule out in structural terms is *not* the odd one out in odor. For example, of the structures 13–15 the last, 15, is the odd one out in chemical terms as it is an alicyclic alcohol, whereas the other two, namely 13 and 14, are both cinnamaldehyde derivatives (Figure 3). However, in terms of odor, it is  $\alpha$ -methylcinna-

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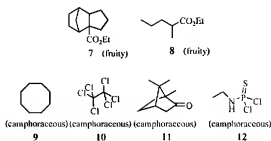


Figure 2. Role of the functional group.

maldehyde (14) which is the odd one out as it has a cinnamon odor<sup>[14]</sup> whereas Lilial (13, also known as Lily Aldehyde and Lilialtal<sup>[1]</sup>) and Florosa or Florol (15)<sup>[4]</sup> both have muguet (lily-of-the-valley) odors. As stated above, the ester group is usually associated with fruity scents, but *tert*-amyl acetate (17) has an odor which is much closer to that of camphor (11) than to the fruity, banana–pear scent of its isomer, *n*-amyl acetate (16; Figure 3).<sup>[4]</sup>

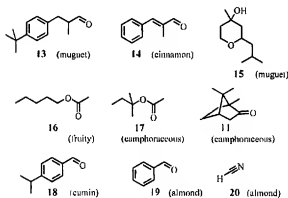


Figure 3. Triads of molecules in which the odd one out structurally is not necessarily the odd one out in odor.

Perhaps the most bizarre and best known of these triads is that involving structures 18–20. Cinnamaldehyde (18)<sup>[12]</sup> as its name suggests, smells of cumin, whereas benzaldehyde (19)<sup>[14]</sup> and hydrogen cyanide (20)<sup>[14]</sup> both smell of almond. Some theories have been proposed to account for the similarity in

odor between 19 and 20, for example, by invoking oligomerization of HCN in the receptor binding site.<sup>[19]</sup> However, the explanation is surely more likely to lie in higher-order neuroprocessing.<sup>[14]</sup>

## 2. Structure–Odor Models

Over the last century, many theories have been proposed relating to the primary events in olfaction and to relationships between molecular structure and odor. The review by Rossiter<sup>[17]</sup> gives an excellent summary of these theories. However, the prediction of odor remains a statistical exercise. For example, Chastrette and De Sainte Laumer developed a model based on a neural network for the prediction of the musk odor of nitrobenzene derivatives.<sup>[18]</sup> Their model gave results that were correct in 77% of test materials. Similarly, Bersuker et al. developed a model for musk activity based on an electron-topological approach.<sup>[19]</sup> Their results were impressive, yet 15 of their set of 362 materials were incorrectly predicted.

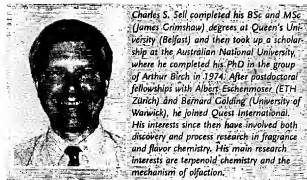
Most structure–odor models are concerned with the character of the odor. However, the commercially important parameters of detection threshold, recognition threshold, and superthreshold intensity of odorants have received much less attention, partly because of the difficulty<sup>[20]</sup> and cost of measurement of these parameters and/or because such models are even more difficult to construct. Nevertheless, detection threshold models are beginning to appear and examples include studies by Kraft on materials with marine<sup>[21]</sup> and musk<sup>[22]</sup> odor characters.

In his review of the subject, Weyerstahl concluded: “Despite numerous excellent studies during the last 30 years the area of structure–odor relationships remains rather confusing.”<sup>[23]</sup>

## 3. The Effect of Structural Modifications

One phenomenon that seriously disrupts attempts to correlate odor properties with molecular structure is that a given structural modification can induce a dramatic change in odor properties in one situation whilst having little or no effect in another. The following list of examples serves to illustrate that this is a general phenomenon that is applicable across a wide range of structural modifications and not just a few isolated instances.

The majority of odorants contain only one strongly polar function in the molecular structure. It is generally believed that this polar group will form a hydrogen bond or some other dipolar attachment to a polar site on an olfactory receptor, with the remainder of the molecule occupying a hydrophobic space in the receptor. Such polar groups have therefore come to be known as osmophoric groups or osmophores,<sup>[22]</sup> and they are used in structure–activity relationships (SARs) as a molecular reference point.<sup>[19,22]</sup> (Occasionally, a second, usually weaker, electron donor or acceptor is also involved.) Structures 21–24 all contain a cyclohexane ring with an osmophoric group at one end and either an isopropyl or *tert*-



butyl group at the other (Figure 4). In dihydrocyclopentyl acetate (21) and *p*-*tert*-butylcyclohexyl acetate (22), the osmophore is an acetate and there is little effect on the odor upon changing an isopropyl group for a *tert*-butyl substituent; Arcander

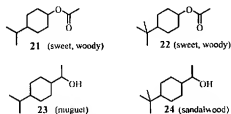


Figure 4. Role of the osmophore.

describes both as being predominantly sweet and woody in character.<sup>[24,25]</sup> However, when the osmophore is the secondary alcohol group of structures 23 and 24, a similar small structural change has a major effect on the odor, taking it from muguet to sandalwood.<sup>[26]</sup>

Similarly, substitution of the *tert*-butyl group of 22 by an isobutyl group to give 25 changes the odor from sweet and woody to a harsh raspberry character,<sup>[27]</sup> whereas the same exchange has little effect on the muguet character of Lilial (13), whose isobutyl analogue Silval (26) has a similar muguet odor (Figure 5).<sup>[28]</sup>

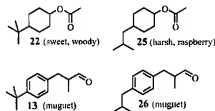


Figure 5. Role of the hydrophobic residue.

Analogous examples also exist in the case of geometric isomers. For instance, in the case of Rositol, the odor is muguet/citrus whether the alcohol function lies *trans* (27) or *cis* (28) to the isobutyl group. However, in the analogues in which the isobutyl group has been replaced by a cyclohexyl substituent, the *trans* isomer 29 has a strong, specifically muguet odor whereas that of the *cis* isomer 30 is much weaker, woody, and only generally floral (Figure 6).<sup>[29]</sup>

The same pattern applies to geometric isomers of double bonds. (Z)-4-Heptenal (31) has a creamy, buttery odor,<sup>[30]</sup> whereas the *E* isomer 32 has an aggressive, green and putty-like odor.<sup>[31]</sup> However, in the case of 2-tetradecenal, both isomers 33 and 34 have fresh, orange odors (although that of 33 is more mandarin-like; Figure 7).<sup>[32]</sup>

Positional isomers around rings are also subject to this phenomenon. The odor of the *meta* isomer 35 of Lilial (13) is reported to be stronger than that of the *para* isomer,<sup>[34]</sup> whereas the odors of both *m*- and *p*-Cyclamen Aldehydes

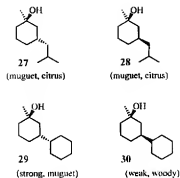


Figure 6. Odors of geometric isomers in rings.

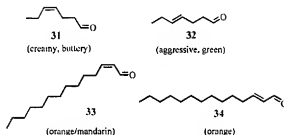


Figure 7. Odors of geometric isomers in olefins.

(36 and 37, respectively) are similar in character and intensity (Figure 8).<sup>[32]</sup> With the dihydrocinnamaldehydes 13 and 35–37, the intensity of the odor varies but the character of all four remains similar. However, in the case of the acylcyclohexenes 38 and 39, the shift from *meta* to *para* substitution results in a change in odor character from the green and fatty notes of 38 to the fruity odor of 39 (Figure 8).<sup>[33]</sup>

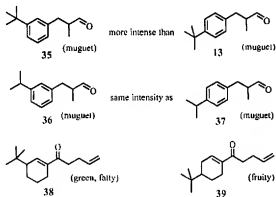


Figure 8. Effect of positional isomers on odor.

The presence or absence of a double bond also provides examples. Linalool (40)<sup>[34]</sup> and dihydrolinalool (41)<sup>[35]</sup> have similar refreshing floral, woody, and citrus odors. However, a similar saturation of a double bond with concomitant

conversion from an allylic alcohol into a saturated alcohol changes the odor from the intense, earthy mushroom character of **42**<sup>[11]</sup> to the sweet, warm, herbaceous, and nutty scent of **43** (Figure 9).<sup>[16]</sup>

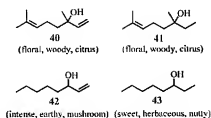


Figure 9. Effect of saturation of a double bond.

The conversion of a primary alcohol into a secondary alcohol by the addition of a methyl group also gives unpredictable results. Geraniol (**44**) is well known for its rosy odor,<sup>[17]</sup> whereas the higher homologue **45** has an intense fungal odor.<sup>[18]</sup> On the other hand, a similar transformation from Sandal Mysore Core (Santacore; **46**) to **47**, the dehydro analogue of Sandalore, has only a relatively small effect on the central sandalwood character (Figure 10).<sup>[11,39,40]</sup>

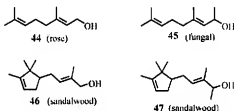


Figure 10. Effect of conversion from primary into secondary alcohols.

As stated above, functional groups are usually important in determining odor character, however, sometimes the exchange of one function for another has little or no effect. In the next three examples, a ketone group is exchanged for the acetate of the corresponding alcohol with three different levels of effect. On going from acetophenone (**48**) to styrallyl acetate (**49**), the odor shifts from sweet hawthorn-like<sup>[41]</sup> to dry, fruity, and green.<sup>[11]</sup> On moving from Patchone (**50**) to *p*-*tert*-butylcyclohexyl acetate (**51**), the degree of change is somewhat less as the odors of both materials have woody characters; that of patchone is very much on the camphoraceous and minty side of wood,<sup>[42]</sup> whereas the odor of **51** has a sweet, almost fruity character (Figure 11).<sup>[29]</sup> At the other end of this spectrum, polywood ketone (**52**) and Polywood (**53**) have similar woody, ambergris odors.<sup>[21]</sup>

Substitutions by a fragment with similar stereoelectronic properties is a common practice in fragrance ingredient discovery, just as it is in drug discovery. For example, when following up on a lead from nature, the isobutenyl group of terpenoid compounds is often substituted by a benzene ring.<sup>[43]</sup> Thus, citronellol (**54**) served as a lead for Mefrosol (also known as Phenoxanol; **55**) and the odors of both

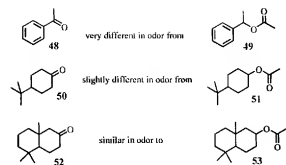


Figure 11. Effect of changing a ketone to an acetate.

compounds have a rosy character.<sup>[11]</sup> However, the green, pungent, herbaceous character of 2-methylhept-2-ene-6-one (**56**)<sup>[44]</sup> is not replicated by the sweet, floral character of benzylacetone (**57**; Figure 12).<sup>[11]</sup>

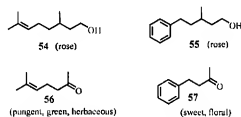


Figure 12. Effect of substitution a fragment with similar stereoelectronic properties.

Another standard substitution is that of a cyclopropane ring for a double bond. The alcohol **46** and ketone **58** both have sandalwood-like odors. Cyclopropanation of both double bonds of **46** produces Javanol (**59**), which is considered to be the strongest sandalwood-scented material known, and both "intermediate" monocyclopropanated species also have predominantly sandalwood characters (Figure 13).<sup>[45]</sup> However, cyclopropanation of one of the double bonds of **58** to give **60** leads to complete loss of the sandalwood-like odor.<sup>[33]</sup>

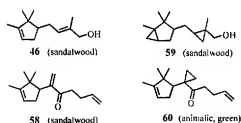








Figure 13. Effect of a cyclopropyl substituent.

Chirality also provides us with many examples of the unpredictability of the effect of changes in molecular structure on the odor of the molecule.<sup>[46]</sup> In the case of Linal (**13**) one enantiomer is odorless,<sup>[47]</sup> whereas the odors of both



enantiomers of the pyrazine **61** are identical in character and threshold.<sup>[98]</sup> The pair of ethers **62** and **63** have identical thresholds of detection but different odor characters (Table 1).<sup>[99]</sup> The odors of the musks (–)-**1** and (+)-**1** have the same character, but the threshold of (–)-**1** is 0.43 ng L<sup>–1</sup> whereas that of its enantiomer (+)-**1** is over twenty times higher at 9.5 ng L<sup>–1</sup>.<sup>[90]</sup> The odors of the enantiomers of dihydro- $\alpha$ -ionone, **64** and **65**, differ in both character and threshold.<sup>[101]</sup>

Table 1: Effect of chirality on the odor of a molecule.

Compound	Odor	Threshold [ng L <sup>–1</sup> ]	Compound	Odor	Threshold [ng L <sup>–1</sup> ]
	woody, pineapple	40		woody, rose	40
	musk	0.43		musk	9.5
	orris	100		violet	31

#### 4. Recent Advances in Understanding Odor Perception

In the 15 years since Weyerstahl's review,<sup>[23]</sup> our ability to predict the odor of a molecule from its molecular structure has not changed much. What has changed, however, is our understanding of why such predictions are so difficult.

The major breakthrough came in 1991 when Buck and Axel identified the gene family that encodes for the olfactory receptor proteins.<sup>[52]</sup> The proteins belong to the family of seven transmembrane G-protein-coupled receptors (GPCRs) and constitute the largest family in the genome. Eight years later, Buck and co-workers<sup>[53]</sup> showed that each of the receptors was broadly tuned, in that it responds to a range of odorant molecules and that, conversely, each odorant molecule triggers a range of receptor types. This report confirmed the hypothesis proposed by Polak that the sense of smell works on a combinatorial basis.<sup>[54]</sup> Buck and Axel received the Nobel Prize in Physiology or Medicine in 2004 for their work.<sup>[55]</sup> and their accounts were published recently.<sup>[56,57]</sup> One might expect that such huge advances in our understanding of the initial stages of odor perception would help us to predict the odor of molecules, but they do not. On the contrary, the breadth of receptor tuning and the large number of receptors involved actually explain why it is so difficult and why it will remain so for a very considerable time to come.

Subsequent developments based on the discoveries of Buck and Axel have enabled molecular biologists to extract the genes involved and to incorporate them into cells in culture and therefore to profile the sensitivity of individual receptor types. One interesting outcome of this discovery is that we now know that olfactory receptors are expressed in sites other than the nose and that they serve quite different functions in these other sites. An example of such work was published by Spehr et al.,<sup>[58]</sup> who showed that the human receptor hOR17-4 (which is found in sperm as well as in the nose) responds to compounds **13**, **37**, and **66–73**, but not to compounds **19** and **74–82** (Figure 14). The strongest response is observed with Bourgeonal (**70**), although this compound is not the natural substrate of the receptor in either the nose or in sperm. To the discovery chemist, this observation points towards a binding site that requires an aldehyde as a hydrogen-bond acceptor and a shape based around that of an alkyl-substituted dihydrocinnamaldehyde. This information can now be used to build a model that could be of use in designing new molecules which could potentially serve as ligands for hOR17-4. One important observation here is that the results confirm that there is not a simple correlation between receptor activity and odor. For example, phenylacetaldehyde (**66**) fires the receptor but its intense green odor<sup>[59]</sup> is a far cry from the muguet character of Lilial,<sup>[101]</sup> which is another agonist.

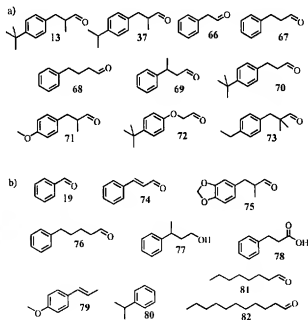


Figure 14. Agonists (a) and non-agonists (b) for hOR17.

Araneda et al.<sup>[60]</sup> studied the receptive range of the rat olfactory receptor OR17. Whereas Spehr et al. carried out direct measurements on the receptor cells, Araneda et al. assessed activity indirectly by measuring activity in the olfactory bulb at the glomerulus which corresponds with receptor neurons that possess OR17. They found that this receptor responds to certain aliphatic aldehydes. From the degree of binding to 90 different test materials, they were able to establish that the binding site seems to recognize only aldehydes. There seems to be a strong steric restriction close to the aldehyde-binding point but much less strict steric requirements further away from it until a limit is reached at a chain length of 11 carbon atoms. Thus, as with hOR17-4, we can now construct a model to aid in molecular design, in this case with an aldehyde-docking area and a hydrophobic pocket with a specific overall length, and which is slightly broader at the end distant from the aldehyde.

The results described above with OR17 and hOR17-4 point towards reasonably selective binding sites, whereas those from other receptors are much less clear-cut. For instance, Sanz et al.<sup>[61]</sup> investigated the specificity of two olfactory receptors, human class I OR52D1 and human class II ORIG1, with rather different results (Table 2). ORIG1 responds strongly to 2-ethylhexan-1-ol (83) and to 1-nonanol (84) but only weakly to 1-heptanol (85) and various

isomeric octanols. It reveals a moderate response to decanoic acid (86) but no response to octanoic acid (87) and only a weak one to nonanoic acid (88). In the aldehyde series, its strongest response is to nonanal (89). With octanal (81) and decanal (90) it elicits only weak responses, whereas with benzaldehyde (19) and Lyrar (91) it responds moderately. Of 16 esters tested, ORIG1 responds strongly only to ethyl isobutyrate (92); its response to the isomeric ethyl butyrate (93) is only weak and that to butyl butyrate (94) is almost zero. Strong responses were also observed to molecules as diverse as methyl thiobutanone (95), benzothiazole (96), and  $\gamma$ -undecalactone (97). Thus ORIG1 seems to be quite selective *within* a class of substrates (for example, alcohols or acids) but not selective *between* classes, as it responds to alcohols, aldehydes, acids, esters, lactones, and a variety of heterocyclic systems. On the other hand, receptor OR52D1 generally responded more weakly to the materials in the same test set of 100 but with a different and equally puzzling pattern. It is difficult to see how one might design a model for a typical substrate for either of these receptors.

Research based on Buck and Axel's work has revealed the primary sequences of all of the human olfactory receptor proteins and now allows us to determine which are expressed in any individual. However, these proteins are proving difficult to work with experimentally and none have yet been

Table 2: Response of ORIG1 receptor to various odorant substrates.

Response				
strong	moderate	weak	none	

isolated in pure form. Model studies are based on extrapolation from the structure of bovine rhodopsin, which is the only GPCR for which an X-ray crystal structure exists. There are a number of assumptions in this extrapolation that must be borne in mind. Rhodopsin is an unusual GPCR in several ways, most significantly in that it requires a cofactor, 11-(Z)-retinal. There is also an assumption about conservation of tertiary structure from the crystalline environment to the membrane environment in which it is active. The putative binding sites in olfactory receptors are based on the binding site of 11-(Z)-retinal in rhodopsin rather than on *in vivo* experimental evidence. Spehr et al.<sup>[90]</sup> showed that activation of hOR-17 by Bourgeonal (70) is inhibited by undecenal (82), a non-agonist, and this result might suggest allosteric interactions and hence multiple binding sites. The role of odor-binding proteins (OBPs) in the olfactory mucosa is not understood and it is not known for certain whether or not they play an active role in olfaction or serve merely to remove excess odorant. However, work such as that of Spehr et al.<sup>[90]</sup> shows that, in the case of sperm or HEK cells, the receptor can be fired without the presence of an OBP.

Nonetheless, some excellent work is being done on building models of putative receptor sites and correlating these with *in vivo* activity. The work of Goddard and co-workers<sup>[92–94]</sup> serves as an illustration. Such work nicely complements the substrate-modeling approach of traditional SAR models.

Traditional SAR and binding-site models are essentially static in nature. A recent paper by Lai et al.<sup>[95]</sup> suggests that this might not be the best approach. Like Araneda et al.,<sup>[90]</sup> they looked at rat OR17 receptors. Lai et al. generated a computer model of the receptor and fitted models of potential ligands into the putative binding site. They then set the whole assembly into normal motion and observed whether or not the ligand remained in the binding pocket. Molecules 81 and 98–102 remained in the binding site, whereas 103 and 104 moved out of the pocket once vibratory motion started (Figure 15). This model correlates with experiment as 81 and 98–102 are all activators *in vivo* whereas 103 and 104 are not. These results suggest that dynamics should be considered in addition to the traditional static stereoelectronic space-fitting approach. Prediction of new structures would be more difficult using a dynamic model and its use as an *in silico* screen prior to *in vivo* evaluation would seem more likely.

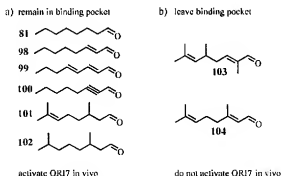


Figure 15. Results of dynamic modeling of OR17.

## 5. Summary and Outlook

From all of the above examples, it is clear that even when the structure of an olfactory receptor is known it is far from certain that one could predict how well any novel potential ligand would bind to it. Facing an array of 350–400 receptors, the task would be even more difficult as a subtle change in structure might affect the binding of any one of the receptors which even a close analogue activates. In other words, the chances of correctly predicting the total pattern of receptor signaling for an odorant molecule are hundreds of times less than doing so for a pharmaceutical target. Furthermore, there are many levels of neurotransmission between the receptors and the cortex, where the signals from the receptor array are eventually interpreted as the phenomenon that we refer to as odor. At each level there are gates with opportunities for interaction between signals from different receptors and the possibility for either reduction or enhancement of individual signal components. All of this would have to be understood in order to know how the initial signal pattern would come together in the higher brain. A subtle change in signal intensity from one receptor type could have a disproportionately large effect on the overall interpretation in terms of odor character, threshold, and/or perceived intensity.

It would therefore seem that consistently accurate prediction of odors will not be possible for a very considerable time and not until a great amount of further research has been completed, the cost of which could not be borne by the flavor and fragrance industry.

In his review, Weyerstahl<sup>[23]</sup> outlined the objectives of structure–odor correlations as being 1) prediction of odors, 2) rational design of odorants, and 3) understanding the mechanism of olfaction. Since then, advances in the biosciences have greatly increased our understanding of the mechanism of olfaction but in a way that does not bode well for Weyerstahl's other two objectives. It would appear that our SAR tools will be refined and improved, although, for the foreseeable future, the prediction of odor will remain only statistical probabilities rather than certainties. There will be plenty of room for surprises and serendipity.

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